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Citation

Laurent, Gaëlle, Natalie J German, Asish K Saha, Vincent CJ de Boer, Frank Fischer, Gina Boanca, Noah Dephore, Bhavapriya Vaitheesvaran, Michael Davies, Steven P Gygi, Deborah M Muio, Irwin J Kurland, Clemens Steegborn, Neil B Ruderman, and Marcia C Haigis. 2012. SIRT4 controls the balance between lipid synthesis and catabolism by repressing malonyl-CoA decarboxylase. BMC Proceedings 6(Suppl 3): P30.

Published Version

doi:10.1186/1753-6561-6-S3-P30

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POSTER PRESENTATION

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SIRT4 controls the balance between lipid synthesis and catabolism by repressing malonyl-CoA decarboxylase

Gaëlle Laurent¹, Natalie J German¹, Asish K Saha², Vincent CJ de Boer^{1,3}, Frank Fischer⁴, Gina Boanca⁴, Noah Dephoure⁵, Bhavapriya Vaitheesvaran⁶, Michael Davies⁷, Steven P Gygi⁵, Deborah M Muoio⁷, Irwin J Kurland⁶, Clemens Steegborn⁴, Neil B Ruderman², Marcia C Haigis^{1*}

From Metabolism, diet and disease
Washington, DC, USA. 29-31 May 2012

Lipid metabolism is highly controlled by the nutritional state of the organism. In this study, we identify the mitochondrial sirtuin, SIRT4, as a critical regulator of lipid homeostasis. We find that SIRT4 represses fatty acid oxidation while promoting lipid anabolism. Mechanistically, SIRT4 regulates this balance by inhibiting malonyl-CoA decarboxylase (MCD), an enzyme that produces acetyl-CoA from malonyl-CoA, a precursor for lipogenesis that also inhibits mitochondrial fat oxidation. We find that SIRT4 is active in nutrient-rich conditions, such as in the fed state. As a consequence, SIRT4 null mice display reduced levels of malonyl-CoA in skeletal muscle and white adipose tissue in the fed state and fail to further lower malonyl-CoA levels during fasting. SIRT4 null mice possess a catabolic signature of lipid metabolism and demonstrate decreased de novo lipogenesis. These studies highlight SIRT4 as a novel regulator of MCD activity and malonyl-CoA levels, providing new insight into the regulation of lipid homeostasis.

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Published: 1 June 2012

doi:10.1186/1753-6561-6-S3-P30

Cite this article as: Laurent et al.: SIRT4 controls the balance between lipid synthesis and catabolism by repressing malonyl-CoA decarboxylase. *BMC Proceedings* 2012 **6**(Suppl 3):P30.

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